

REMARKS

REJECTION UNDER 35 USC §112

Applicants respectfully submit that the term "measurement period" is sufficiently clear from both the specification and knowledge commonly held in the art to particularly point out and distinctly claim that which applicants consider to be their invention. As set forward in the specification, beginning on page 2, line 44, and extending to page 3, line 23, at least two measurements of IL-6 serum levels are taken, with "[t]he second, later measurement ... obtained within a period of from 30 minutes to 48 hours after the first" (p.3:14-15). This period of time between which the first and second measurements are taken is logically referred to as the "measurement period," as indicated in the parenthetically enclosed phrase on page 3, line 16. Applicants respectfully submit that one of ordinary skill in the art would understand the meaning of the term "measurement period" from both this disclosure, and from the knowledge commonly held in the art.

REJECTION UNDER 35 USC §103(A)

Claims 1-7 are rejected under 35 USC §103(a) and the doctrine of obviousness-type double patenting, based on Stenzel et al. (US 6,235,281 and WO 95/20978) in view of Kraghsbjerg et al. (Dynamics of Blood Cytokine Concentrations in Patients with Bacteremic Infections, *Scand. J. Infect. Dis.*, 28391-398 (1996)). Applicants respectfully traverse these rejections. To establish *prima facie* obviousness, the examiner must show in the prior art a teaching or suggestion of each claim element, some suggestion or motivation to make the claimed invention, and a reasonable

expectation for success in doing so (see, e.g., *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). These requirements have not been met in the examiner's present rejection.

The examiner characterizes the present claims as being drawn to use of TNF antagonists for treatment of septic disorders in which IL-6 serum levels are elevated (ppr.10, pp.3, 5, 7). However, this characterization of the presently claimed invention is incomplete. The present claims not only require that the IL-6 serum level in the patient be elevated, but also require that "the serum level of [IL]-6 *increases* in a measurement period of at least thirty minutes" (claim 1, emphasis supplied). This additional requirement that the serum level increase is a necessary criterion for successfully identifying patients to whom TNF antagonists can be administered with heightened effect.

As the examiner correctly indicates, Stenzel et al. (both references) teaches treatment of septicemia patients having IL-6 levels above 1000 pg/ml using a TNF antagonist. Further as correctly noted by the examiner, Stenzel neither describes a change in IL-6 levels, nor measurement of such a change in septicemia patients. Following the preceding paragraph, we would point out that Stenzel also omits any reference to the relevance of the directionality of change in serum IL-6 levels over the course of the measurement period.

Kraghsbjerg et al. is utilized by the examiner to demonstrate monitoring of IL-6

serum levels over the course of treatment, and correlation of high IL-6 levels with "risk of a fatal course" (ppr.10, p.4). In doing so, the deficiencies noted by the examiner in Stenzel are met. However, the additional deficiency pointed out by the applicants is not addressed. Kraghsbjerg does not indicate anywhere in the reference the possibility that treatment with TNF antagonists would be desirable or particularly effective in cases where IL-6 serum levels are increasing. The only discussion of change in IL-6 serum levels is as follows:

IL-6. Apart from 2 fatal cases, IL-6 levels were maximal on admission and declined progressively. When all etiological groups were considered together, levels had declined significantly after 4 ($p=0.03$), 12 ($p=0.01$), 18 ($p=0.006$), and 24 h ($p=0.003$) in survivors. In the same group the mean time from maximum value to a concentration <100 pg/ml was 27 h.

(Kraghsbjerg, p.394.) In only two cases, both of which were fatal, did IL-6 levels increase during any one measurement period (all others "declined progressively"). The Kraghsbjerg reference makes no correlation between such an increase and successful treatment of the septic disorder.

Accordingly, applicants respectfully submit that one of skill in the art would not have sufficient basis from the combined disclosures of Stenzel and Kraghsbjerg to find motivation or potential for success in treating septic disorders in which the IL-6 level increases during the measurement period. Neither reference gives any indication that of the overall group of patients suffering from septic disorders treatment of those showing an increase in IL-6 serum levels would be particularly effective. Nothing in the present record supports the argument that such selective treatment is obvious. In view of these points, applicants respectfully request that the rejection of claims 1-7 under 35



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USC §103(a) and under the doctrine of obviousness-type double patenting been withdrawn.

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CONCLUSION

In view of the foregoing remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

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Respectfully submitted,
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